Docket: 1073.060

Amendments

In the Claims:

Please amend claims 1, 4, 7, 9-11, 14, 17-21, 24 and 27-30 as follows:

Sub C1 B1

(Twice Amended) 1. A computer-aided method of docking a molecule to a protein having a binding site, said method comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the molecule;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the molecule to obtain at least one position of the molecule relative to the protein in a protein-ligand complex; and

optimizing the at least one position of the molecule while allowing translation, orientation and rotatable bonds of the molecule to vary, and while holding the protein fixed;

wherein said method is not an incremental construction method.

Sub C3 B2

(Twice Amended) 4. The method of claim 1, wherein said performing the pre-docking conformational search comprises:

randomly generating a plurality of conformations of the molecule;

minimizing a strain of each conformation of the plurality of conformations;

using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the molecule.

Sub C4 B3

(Amended) 7. The method of claim 1, wherein said matching comprises:

matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

using the unique rigid body transformation to place the at least one solution conformation of the molecule into the binding site of the protein.

B4

(Twice Amended) 9. The method of claim 1, wherein multiple positions of the molecule are obtained, and said optimizing step comprises :

eliminating each position of the molecule having a predetermined percentage of atoms with a steric clash;

Sub C5

ranking remaining positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, clustering the positions of the molecule and selecting a top number n of positions; and

optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the molecule to vary.

(Twice Amended) 10. The method of claim 9, wherein said optimizing comprises optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the molecule to vary.

(Twice Amended) 11. A computer-aided system for docking a molecule to a protein having a binding site, said system comprising:

means for performing a pre-docking conformational search to generate multiple solution conformations of the molecule;

means for generating a binding site image of the protein, said binding site image comprising multiple hot spots;

means for matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the molecule to obtain at least one position of the molecule relative to the protein in a protein-ligand complex; and

means for optimizing the at least one position of the molecule while allowing translation, orientation and rotatable bonds of the molecule to vary, and while holding the protein fixed;

wherein said system does not use an incremental construction method.

(Twice Amended) 14. The system of claim 11, wherein said means for performing the pre-docking conformational search comprises:

means for randomly generating a plurality of conformations of the molecule;

means for minimizing a strain of each conformation of the plurality of conformations;

means for using the strain and a solvent accessible surface area of each conformation to rank the conformations; and

means for clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the molecule.

(Amended) 17. The system of claim 11, wherein said means for matching comprises:

means for matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

means for defining a match, said match determining a unique rigid body transformation; and

means for using the unique rigid body transformation to place the at least one solution conformation of the molecule into the binding site of the protein.

(Twice Amended) 18. The system of claim 17, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

$$I(R, T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Twice Amended) 19. The system of claim 11, wherein multiple positions of the molecule are obtained, and said means for optimizing comprises :

means for eliminating each position of the molecule having a predetermined percentage of atoms with a steric clash;

means for ranking remaining positions of the molecule using an atom pairwise score with a desired atom score cutoff, said atom pairwise score comprising a hydrogen bonding potential score or a steric potential score;

after ranking, means for clustering the positions of the molecule and selecting a top number n of positions; and

means for optimizing each of the n positions, allowing the translation, orientation and rotatable bonds of the molecule to vary.

(Twice Amended) 20. The system of claim 19, wherein said means for optimizing comprises means for optimizing each position of the n positions using a Broyden-Fletcher-Goldfarb-Shanno (BFGS) optimization algorithm with said atom pairwise score, allowing the translation, orientation and rotatable bonds of the molecule to vary.

(Twice Amended) 21. At least one program storage device readable by a machine, tangibly embodying at least one program of instructions executable by the machine to perform a method of docking a molecule to a protein having a binding site, said method comprising:

performing a pre-docking conformational search to generate multiple solution conformations of the molecule;

generating a binding site image of the protein, said binding site image comprising multiple hot spots;

matching hot spots of the binding site image to atoms in at least one solution conformation of the multiple solution conformations of the molecule to obtain at least one position of the molecule relative to the protein in a protein-ligand complex; and

optimizing the at least one position while allowing translation, orientation and rotatable bonds of the molecule to vary, and while holding the protein fixed ;

B7

wherein said method is not an incremental construction method.

(Twice Amended) 24. The at least one program storage device of claim 21, wherein said performing the pre-docking conformational search comprises:

B8

Sub C2

randomly generating a plurality of conformations of the molecule;

minimizing a strain and a solvent accessible surface area of each conformation of the plurality of conformations;

using the strain of each conformation to rank the conformations; and

clustering the conformations and retaining a desired top number of clusters of conformations, said retained top number of clusters of conformations comprising said multiple solution conformations of the molecule.

B9 **(Amended)** 27. The at least one program storage device of claim 21, wherein said matching comprises:

matching atoms of the at least one solution conformation to appropriate hot spots of the protein by positioning the at least one solution conformation as a rigid body into the binding site image;

defining a match, said match determining a unique rigid body transformation; and

Sub C13 using the unique rigid body transformation to place the at least one solution conformation of the molecule into the binding site of the protein.

B10 **(Twice Amended)** 28. The at least one program storage device of claim 27, wherein said determining the unique rigid body transformation comprises determining the unique rigid body transformation that minimizes:

Subst C14

$$I(R, T) = \sum_{j=1}^{3} \left| H_j - RA_j - T \right|^2$$

where:

$I(R,T)$ = rms deviation between a j^{th} hot spot and a j^{th} atom of the at least one solution conformation;

H_j = a position vector of a j^{th} hot spot of the protein;

A_j = a position vector of a j^{th} atom of the at least one solution conformation;

R = a 3×3 rotation matrix; and

T = a translation vector.

(Twice Amended) 29. The at least one program storage device of claim 21, wherein multiple positions of the molecule are obtained, and said optimizing step comprises :

eliminating each position of the molecule having a predetermined percentage of atoms with a steric clash;